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Date: 23 may 2002

Destination: Agent

Address:

DEX0285_163 Antigenicity Index(Jameson-Wolf)

positions AI avg length

10-24 1.21 15

DEX0285_167 Antigenicity Index(Jameson-Wolf)

positions AI avg length

35-54 1.30 20

DEX0285_169 Antigenicity Index(Jameson-Wolf)

positions AI avg length

92-104 1.03 13

DEX0285_183 Antigenicity Index(Jameson-Wolf)

positions AI avg length

14-56 1.12 43

DEX0285_184 Antigenicity Index(Jameson-Wolf)

positions AI avg length

76-85 1.08 10

DEX0285_196 Antigenicity Index(Jameson-Wolf)

positions AI avg length

14-28 1.10 15

DEX0285_197 Antigenicity Index(Jameson-Wolf)

positions AI avg length

82-104 1.27 23

57-69 1.27 13

138-151 1.21 14

111-131 1.06 21

DEX0285_199 Antigenicity Index(Jameson-Wolf)

positions AI avg length

5-19 1.01 15

DEX0285_203 Antigenicity Index(Jameson-Wolf)

positions AI avg length

36-46 1.00 11

In addition, the following helical regions were also assigned:

DEX0275_33 PredHel=1 Topology=i69-91o

DEX0275_42 PredHel=1 Topology=i7-29o

DEX0275_44 PredHel=1 Topology=i7-26o

DEX0275_47 PredHel=1 Topology=i44-66o

DEX0275_48 PredHel=1 Topology=o20-42i

Example 6: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA is isolated from individual patients or from a family of individuals that have a phenotype of interest. cDNA is then generated from these RNA samples using protocols known in the art. *See*, Sambrook (2001), *supra*. The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO: 1 through 29. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky *et al., Science* 252(5006): 706-9 (1991). *See also* Sidransky *et al., Science* 278(5340): 1054-9 (1997).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing. PCR products is cloned into T-tailed vectors as described in Holton *et al., Nucleic Acids Res.*, 19: 1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements may also be determined. Genomic clones are nick-translated with digoxigenin deoxyuridine 5' triphosphate (Boehringer Manheim), and FISH is performed as described in Johnson *et al., Methods Cell Biol.* 35: 73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C-and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ)

and variable excitation wavelength filters. *Id.* Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 7: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

Antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 μg/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described above. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced. The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide. Next, 50 μl of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate. 75 μl of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution are added to each well and incubated 1 hour at room temperature.

The reaction is measured by a microtiter plate reader. A standard curve is prepared, using serial dilutions of a control sample, and polypeptide concentrations are plotted on the X-axis (log scale) and fluorescence or absorbance on the Y-axis (linear scale). The concentration of the polypeptide in the sample is calculated using the standard curve.

Example 8: Formulating a Polypeptide

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide

alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 , μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 μg/kg/hour to about 50 mg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semipermeable polymer matrices in the form of shaped articles, e. g., films, or microcapsules. Sustained-release matrices include polylactides (U. S. Pat. No.3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22: 547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15: 167-277 (1981), and R. Langer, Chem. Tech. 12: 98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE Epstein

et al., Proc. Natl. Acad. Sci. USA 82: 3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U. S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, I. e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides. Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e. g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e. g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1 % (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container (s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 9: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides.a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 μg/kg of the polypeptide for six consecutive days. Preferably, the

polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided above.

Example 10: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided above.

Example 11: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e. g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks. pMV-7 (Kirschmeier, P. T. et al., DNA, 7: 219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5'and 3'end sequences respectively as set forth in Example 1. Preferably, the 5'primer contains an EcoRI site and the 3'primer

includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB 101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+aml2 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media.

If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 12: Method of Treatment Using Gene Therapy-*In Vivo*

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide.

The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known

in the art, see, for example, W0 90/11092, W0 98/11779; U. S. Patent 5,693,622; 5,705,151; 5,580,859; Tabata H. et al. (1997) Cardiovasc. Res. 35 (3): 470-479, Chao J et al. (1997) Pharmacol. Res. 35 (6): 517-522, Wolff J. A. (1997) Neuromuscul. Disord. 7 (5): 314-318, Schwartz B. et al. (1996) Gene Ther. 3 (5): 405-411, Tsurumi Y. et al. (1996) Circulation 94 (12): 3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P. L. et al. (1995) Ann. NY Acad. Sci. 772: 126-139 and Abdallah B. et al. (1995) Biol. Cell 85 (1): 1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by

the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 μg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about

0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e. g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice.

The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 13: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e. g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i. e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40: 691-698 (1994); Carver et al., Biotechnology (NY) 11: 1263-1270 (1993); Wright et al., Biotechnology (NY) 9: 830-834 (1991); and Hoppe et al., U. S. Patent 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82: 6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56: 313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3: 1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e. g., Ulmer et al., Science 259: 1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm mediated gene transfer (Lavitrano et al., Cell 57: 717-723 (1989); etc. For a review of such techniques, see Gordon,"Transgenic Animals," Intl.

Rev. Cytol. 115: 171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380: 64-66 (1996); Wilmut et al., Nature 385: 810813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, I. e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e. g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89: 6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265: 103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, in situ hybridization analysis, and reverse transcriptase-PCR

(rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 14: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E. g., see Smithies et al., Nature 317: 230-234 (1985); Thomas & Capecchi, Cell 51: 503512 (1987); Thompson et al., Cell 5: 313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such

approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e. g., see Thomas & Capecchi 1987 and Thompson 1989, supra). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e. g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (I. e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e. g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e. g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e. g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e. g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U. S. Patent 5,399,349; and Mulligan & Wilson, U. S. Patent 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the

development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

All patents, patent publications, and other published references mentioned herein are hereby incorporated by reference in their entireties as if each had been individually and specifically incorporated by reference herein. While preferred illustrative embodiments of the present invention are described, one skilled in the art will appreciate that the present invention can be practiced by other than the described embodiments, which are presented for purposes of illustration only and not by way of limitation. The present invention is limited only by the claims that follow.

CLAIMS

We claim:

1. An isolated nucleic acid molecule comprising

(a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 30 through 55;

(b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1 through 29;

(c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule having at least 60% sequence identity to the nucleic acid molecule of (a) or (b).

2. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a cDNA.

3. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is genomic DNA.

4. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a mammalian nucleic acid molecule.

5. The nucleic acid molecule according to claim 4, wherein the nucleic acid molecule is a human nucleic acid molecule.

6. A method for determining the presence of a lung specific nucleic acid (LSNA) in a sample, comprising the steps of:

(a) contacting the sample with the nucleic acid molecule according to claim 1 under conditions in which the nucleic acid molecule will selectively hybridize to a lung specific nucleic acid; and

(b) detecting hybridization of the nucleic acid molecule to a LSNA in the sample, wherein the detection of the hybridization indicates the presence of a LSNA in the sample.

7. A vector comprising the nucleic acid molecule of claim 1.

8. A host cell comprising the vector according to claim 7.

9. A method for producing a polypeptide encoded by the nucleic acid molecule according to claim 1, comprising the steps of (a) providing a host cell comprising the nucleic acid molecule operably linked to one or more expression control sequences, and (b) incubating the host cell under conditions in which the polypeptide is produced.

10. A polypeptide encoded by the nucleic acid molecule according to claim 1.

11. An isolated polypeptide selected from the group consisting of:

(a) a polypeptide comprising an amino acid sequence with at least 60% sequence identity to of SEQ ID NO: 30 through 55; or

(b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1 through 29.

12. An antibody or fragment thereof that specifically binds to the polypeptide according to claim 11.

13. A method for determining the presence of a lung specific protein in a sample, comprising the steps of:

(a) contacting the sample with the antibody according to claim 12 under conditions in which the antibody will selectively bind to the lung specific protein; and

(b) detecting binding of the antibody to a lung specific protein in the sample, wherein the detection of binding indicates the presence of a lung specific protein in the sample.

14. A method for diagnosing and monitoring the presence and metastases of lung cancer in a patient, comprising the steps of:

(a) determining an amount of the nucleic acid molecule of claim 1 or a polypeptide of claim 6 in a sample of a patient; and

(b) comparing the amount of the determined nucleic acid molecule or the polypeptide in the sample of the patient to the amount of the lung specific marker in a normal control; wherein a difference in the amount of the nucleic acid molecule or the polypeptide in the sample compared to the amount of the nucleic acid molecule or the polypeptide in the normal control is associated with the presence of lung cancer.

15. A kit for detecting a risk of cancer or presence of cancer in a patient, said kit comprising a means for determining the presence the nucleic acid molecule of claim 1 or a polypeptide of claim 6 in a sample of a patient.

16. A method of treating a patient with lung cancer, comprising the step of administering a composition according to claim 12 to a patient in need thereof, wherein said administration induces an immune response against the lung cancer cell expressing the nucleic acid molecule or polypeptide.

17. A vaccine comprising the polypeptide or the nucleic acid encoding the polypeptide of claim 11.

SEQUENCE LISTING

<110> Macina, Roberto
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Chen, Sei-Yu
Sun, Yongming
Liu, Chenghua
Turner, Leah
diaDexus, Inc.

<120> Compositions and Methods Relating to Lung Specific Genes and Proteins

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<211> 251
<212> DNA
<213> Homo sapien

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<210> 13
<211> 624
<212> DNA
<213> Homo sapien

<400> 13
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<211> 1623
<212> DNA
<213> Homo sapien

<220>
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<223> a, c, g or t

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caa 1623

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<211> 393
<212> DNA
<213> Homo sapien

<400> 15
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ccctttttt ccccccgggg gggggggtg gtggggagca gtaaacatca ggcccaggaa 180

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<211> 839
<212> DNA
<213> Homo sapien

<400> 16
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cttataacaa gcgcagtgcg taaactattt caagtgacat acgcatggat aggtctctaa 480

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<210> 17
<211> 1176
<212> DNA
<213> Homo sapien

<400> 17
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<211> 1069
<212> DNA
<213> Homo sapien

<400> 18
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tgccaggtaa ccacgcatcc actccagagt gaacggtggc cagaggttgg acaacggtca 120

catgtgcccg tgtttagtct gcgccacgtt tagaatactt gatggctatc tgagcgtggg 180

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tgcactggga attcactggt acatacaaca acactctatg cgccagtca 1069

<210> 19
<211> 637
<212> DNA
<213> Homo sapien

<400> 19
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tggctgtgac aaacaccgga accggaagaa caaacga 637

<210> 20
<211> 895
<212> DNA
<213> Homo sapien

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<221> misc_feature
<222> (365)..(365)
<223> a, c, g or t

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<210> 21
<211> 506
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (276)..(276)
<223> a, c, g or t

<220>
<221> misc_feature
<222> (462)..(462)
<223> a, c, g or t

<400> 21
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<210> 22
<211> 5387
<212> DNA
<213> Homo sapien

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caggcgtgtg catggggcca ggtgtgcacg tggatgcccg ggtgagtgtg tgtgcatgca 4080

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gcatgggaca gggcagcccg atgccagctg gcctacctga ctgtgccagg ggccctgccc 4440

ccaccctctc aggatggcct agacttgggg aacagagccg ggtggggttg cagcccggag 4500

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cacccaggag ggaggtggca cttcttaacc tgtacagttt tattgtacca agagactcgc 4680

cccgcccctg tatcataagc ctttaaatgg agtcaacttt ttaattatat atataaagat 4740

aaatatatat aaatatatat ataaactttt taaaactgtg aaaaatagct atgaaattat 4800

aaaaaaaaaa cattctgacg tgcagaatat tatttttttat ttcctgttag attatagtgt 4860

ctagcaccgg cttcaccggc ctcccagtcc ccagcacacc ccccgcccac cccgccaagt 4920

gtactgtact caccccccag gatagagaag tgtttgttag ggagagaaga gggagaggca 4980

ggagccggcc caagcccagg gtccctgctt gggccccaga aagcacttaa ccaggcccca 5040

agccttcaag ggaaaccaag gcctcaacca gacaatcttg agggaaggaa aagccagact 5100

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aaataaaatt gtctggagtg gtttatttca ggggctggag taggggtggt gtctgggggc 5280

attctgccat atcagggcac caagaagcag gattcgactg gaagaagttg ggtgccacgc 5340

gtgcaggggc ggtgacccca tgcagccatc taaatgagct catcggc 5387

<210> 23
<211> 361
<212> DNA
<213> Homo sapien

<400> 23
tcatataggg cgcatggtca tctagatcat gctcgagcgg cgcattgtga tggatggtcg 60

cggccgaggt ccggccgagg tacatttatt taggagtggg tttcgtgggg gtaggtgata 120

aaaattagga tcagttgaag aaaattgaag aaactaggat cagtaagaga aactgtttgc 180

tttacctgaa tttaactatg aaaacacact taacaatctt acacgtttct agatattaag 240

tgaatatgta actcctgtcc atgggtagat gtgtatcttt gacttctgta attatttttg 300

atattctatc agtgtattat gagactctgg cctccctgca gatcttctaa gaaccacact 360

a 361

<210> 24
<211> 1682
<212> DNA
<213> Homo sapien

<400> 24
gtggcaattc ccccacttac acacaatctt tctgcagttg ctcccagcat taattctgga 60

atggggactg agactatacc aattcagggt tacagagtgg atgagaaaac taagaagtgt 120

tctattccat ttgttaaacc gaacagacat tccccatcag gcatttataa cattaatgtg 180

accacattag tctctagtga aaaaaacctc tttgggcaag taagaaaaga agagaatact 240

ccaggacaga tgtccgtttg cctgaactaa actataatca tctccctgaa ctaagagcac 300

tgggaggcat agctcgaaat tccaggctaa caaagaaaga gagcaaaatt ctttcagaat 360

ctcgaattcc ttctctggct gctattgacc tgcacacccc cagtattaca ttacatcagg 420

tatcaggacc tcccctgtca gatgattcag gggctgattt gcctcaaatg gaacaccagc 480

actgagaacc attttggttc tgaactggat gatgctcttg cacttgagat gacatcttct 540

tgcagcaaga gtgctgatat cccaagagga gagattcatg gttttgatca tttccttctg 600

aactgcctgc attttctgag gaaggccttc tagaagaagg aaagacaaag acttccaaat 660

gtttcaaagg aagattgaac aaatggccct ccccaactgt tatcccatta cctttcacgt 720

ccaccgatgc tatttcaaga catatccagt ggaataacag tgatatggtt cttgttacat 780

gaatgtgtat ttactgttag gagattgtat attttaagtt accatgatta aaagtgtgta 840

aaaaaggggg acagagagaa atactataaa aggccatgtt actcatgcat tgaactttgt 900

gtgttttctg tataaatgtg tacatttatt taggagtggg tttcgtgggg gtaggtgata 960

aaaattagga tcagttgaag aaaattgaag aaactaggat cagtaagaga aactgtttgc 1020

tttacctgaa tttaactatg aaaacacact taacaatctt acacgtttct agatattaag 1080

tgaatatgta actcctgtcc atgggtagat gtgtatcttt gacttctgta attatttttg 1140

atattctatc agtgtattat gagactctgg cctccctgca gatcttctaa gaaccacact 1200

aatgcaagct tgacagagaa acctctttcg aatgacttac tacaactctg gcattggtta 1260

gttccatgta ttgtaagatt ctggtgctaa tgctccatac agaattgatc aggactgatt 1320

actcttctgt ggaccaattg ctattgaact acccagctga agagggtttg gggagagaac 1380

gttcattatt atggactcca cttttgtccc ctggtagttt aagggtgata ctagaatcca 1440

gagaagttcc tgtctccttg tggcctcaaa cactcaggcc gtctcaaaag cttttcacca 1500

aggtgcaaaa tcatttacct gcattccaca catcttttcc aatgcatgga tccaaaactt 1560

tttaggtggg aggaataaac taagttggct acaggttctt gatttctggg tttctacaca 1620

tgctctgcat ttatcatttt agagaatggt tgtttaggga accagaattt gtgagttttt 1680

tt 1682

<210> 25
<211> 718
<212> DNA
<213> Homo sapien

<400> 25
cggccgaggt accagagaac atacagtaaa taatgatttt tacatattga agttgcagtt 60

gttgactgtg atgttgaaga tgtcttcaga cagtagttca tactgcattc cacacttgag 120

gctcaagtga ttggagtgat ttctgcaatt actagtttgt tctataacta agactgtttg 180

ttggtctctg catatacttt caggtcatta aatgctacag aaatgagaaa tgaaatacaa 240

acttttaac tcctactcag atgtccaaac agcttcttag ttcctgtcag atcagtaata 300

atactgggtt tggtctttct taaaccaagc ataatcctgc ttatcttaga atgaaacagt 360

attcctattc agaggtaaat agagttaacc tttactcgtg taatttttat tgttgtttta 420

ccatttcatg gtgttcatac tagccccctt tccttttccct ctaagtgact gctgaggttc 480

tcaccatttc agaataaaat tcttgtcctt tgaggttgga aatttaatga taatgaaaaa 540

ctgtatgtgt cagtatactt aaaaggaaag gttatatcat tctcctcatt tggatgtaaa 600

atttacctgt tagagaacac attggaatta tagaacagaa acacaccccc aaacacacgg 660

ctgggcgtaa ccagggccaa agcggcccgg ggtgaatggt atccgcccca aatccatc 718

<210> 26
<211> 708
<212> DNA
<213> Homo sapien

<400> 26
ggatacacag aatgatcata tatgggccat gttatctaga tgcatgctcg agccggcgct 60

aatgtgatgg atggtcgcgg cgaggtacca gacatgctca aaatgtgctt tcccgttatc 120

tttcagaacc caccaccagg aaaccaaaac ggaccccact ctgagagttc catgatgaag 180

gtgtttaatg aaatcacatt aacccctaag taaaggcagt agatgaaatt atccattatc 240

ttttgtctct tttttttca tagtgtgaga ctacgattgg caaagtggga aaacggacac 300

ccaactcatt tgattagcag aataaatggt gtccattaaa tccctcctct ttgaaagtta 360

tgtgcatggc ccagcagtgg tacgctttag tgccctgcaa ctcccagaca ctttcgggag 420

gccgatggca gaaaggactc gcttgagccc aggagtccga gcaccagcct gggcaactta 480

cgtagggacc ccatctcgtg gttttcttct tttgtacgaa aagaagcaga tttctgtggc 540

gaagacgcta ttgcagacca caagggaggc tcataggaac actgtctcat attgattact 600

ctatgagaag aaactcccgt gtatggaaag ggggcactga gagatctggg cgctcgagag 660

aaacagtggg ggacgcacag ggccggataa gatccaagcc cctattat 708

<210> 27
<211> 1026
<212> DNA
<213> Homo sapien

<400> 27
ggtcaaagcg ggaaaccaaa gagtatgtgg tatccatatt cgttgcaaaa atgataatta 60

ctggaatttt ccaaacatca aasgaagggg gatcaatggt taccactatc gttttcagcc 120

aatatacaga tgttcgctca aggtctaggt tttatttcta catagtagta ttcacatgag 180

ttccctattc tgaagtatta tcaaaacgag gacccttgaa ggtcgagccc agcttgtctt 240

gacttcaaag atgacacagc agccaaccta gaatcctggc ttgctgcttg agtcctagaa 300

atcatgtctt ctcatgtttt acaacaagct gtgtctctga aaactaaaat cagacttcag 360

attcctctga aacagttctg gttcccaagc atccgcacca tggtacccag acatgctcaa 420

aatgtgcttt cccttatctt tcaaaaccca ccaccaggaa accaaaacgg accccactct 480

gagagttcca tgatgaaggt gtttaatgaa atcacattaa cccctaagta aaggcagtag 540

atgaaattat ccattatctt ttgtctcttt ttttttcata gtgtgagact acgattggca 600

aagtgggaaa acggacaccc aactcatttg attagcagaa taaatggtgt ccattaaatc 660

cctcctcttt gaaagttatg tgcatggccc agcagtggta cgctttagtg ccctgcaact 720

cccagacact ttcgggaggc cgatggcaga aaggactcgc ttgagcccag gagtccgagc 780

accagcctgg gcaacttacg tagggacccc atctcgtggt tttcttcttt tgtacgaaaa 840

gaagcagatt tctgtggcga agacgctatt gcagaccaca agggaggctc ataggaacac 900

tgtctcatat tgattactct atgagaagaa actcccgtgt atggaaaggg ggcactgaga 960

gatctgggcg ctcgagagaa acagtggggg acgcacaggg ccggataaga tccaagcccc 1020

tattat 1026

<210> 28
<211> 406
<212> DNA
<213> Homo sapien

<400> 28
gaagatgact catatagggc gatggttcaa catagatgca tgctcgagcg gcgcgttgtg 60

atggatgcgt ggtcgcggcc gaggtactcc acttcaaatt tcccaagaaa tcagaagaat 120

ggtgaacaag tgctggtttc acaatactca gcaagtgttt acacattggg ccaaggacag 180

atttttcctg gagaaggatt ttaccactgc caccatcttg aaattcttca tcgtttggaa 240

cacagagcca tagattttca tttctgcact cagctctgtt ctgagaccgg ggccataggg 300

gttcttggag agacagggca gatggaagaa gtggaaggca tctgcacact gtagagtgcc 360

tttaagccac ccccattgcc tgagttgttt tccttttta caaatg 406

<210> 29
<211> 818
<212> DNA
<213> Homo sapien

<400> 29
gcttttcgtt gttgagcgtc acttaaattc gtgtcatttc atgttggtac aggtactcca 60

cttcaaattt cccaagaaat tcagaagaat tgtgaacaag ttgctggttt cacaatactc 120

agcaagtgtt tacacattgg gccaaggaca gatttttcct ggagaaggat tttaccactg 180

ccaccatctt gaaattcttc atcgttttgg aacacagagc catagatttt catttctgca 240

ctcagctctg ttctgagacc ggggccatag gggttcttgg agagacaggg cagatggaag 300

aagtggaagg catctgcaca ctgtagagtg cctttaagcc acccccattg cctgagttgt 360

tttccttttt tacaaatgaa gcttgttctt ttctgggtct ctccaaggtg gagtgtagga 420

gggcagtgtt ttccgtagcc tctggctcgt gccgcgctct cagactcttc agttctcctc 480

acccacacga gcccaatgag gtaggccttt ttattccatc ttgcagacaa agaaacgatt 540

actcagggtt gataaacacc acccaagatc tcatgggagg aaggaacaga gatgaaaata 600

aaatgcaagg ctgtgtaagt ccaacaaata tgccacatcc atgtcacctc tggggtctga 660

tccagcctct caacaaccac cgtcacccct caacaggcag gtgacagtgg cgagacggcc 720

cagcccagca acaggctccc ccattgcagt gccattgcta tgccagagga cacaaacccc 780

agaccttgac tcctcctcac agaccctgaa cagctaga 818

<210> 30
<211> 57
<212> PRT
<213> Homo sapien

<400> 30

Met Leu Trp Pro Arg Leu Ser Leu Ser Arg Thr Pro Pro Val His Leu
1 5 10 15

Ser Arg Cys Asp Thr Arg Arg Arg Arg Leu Ser Glu Pro Leu Pro Lys
20 25 30

Ser Val Arg Gly Glu Ile His Arg Ala Cys Glu Arg His Thr Lys Cys
35 40 45

Pro Val Ala Leu Ile His Tyr Ile Ile
50 55

<210> 31
<211> 80
<212> PRT
<213> Homo sapien

<400> 31

Met Ser Tyr Lys Asn Gln His Thr Lys Gln Thr Glu Gln Phe Arg Ser
1 5 10 15

Leu Cys Tyr Ser Leu Pro Asp Leu Arg Ser Tyr Cys Leu Ala Tyr Pro
20 25 30

Pro Ser Thr Tyr Leu Cys Tyr Phe Leu Ser Asn Ile Gln His Ile Pro
35 40 45

His Thr Asn Ile Thr Asn Arg Ser Thr Ser Gln Gln Arg Val Ile Tyr
50 55 60

His Ser Ser Leu Thr Ala Leu Val Thr Ile Leu Asn His Pro Gln Thr
65 70 75 80

<210> 32
<211> 41
<212> PRT
<213> Homo sapien

<400> 32

Met Cys Val Thr Arg Ser Leu Leu Asn Cys Leu Tyr Arg Ile Pro Trp
1 5 10 15

Leu Glu Ser His Asp Cys Ser Phe Gly Ser Ala Pro Glu His Cys Thr
20 25 30

Glu Thr Ala Cys Val Gln Gly Val Gly
35 40

<210> 33
<211> 135
<212> PRT
<213> Homo sapien

<400> 33

Met Met Ser Ser Ser Ala Ser Pro Leu Ser Leu Pro Leu Ser Leu Trp
1 5 10 15

Arg Phe Ser Thr Leu Pro Ala Leu Pro Arg Ala Gln Phe Pro Pro Asp
20 25 30

Pro Thr Lys Val Lys Gly Glu Glu Glu Lys Arg Gly Arg Gly Ser Asp
35 40 45

Ala Thr Ser Val Leu His Leu Val Ala Glu Arg Glu Gly Pro Thr Arg
50 55 60

Asp Arg Gly Ser Leu Cys Val Cys Val Cys Val Cys Val Cys
65 70 75 80

Val Cys Val Cys Val Leu Arg Trp Ser Leu Ala Leu Ser Pro Arg Leu
85 90 95

Glu Gly Ser Gly Ala Ile Leu Ala His Cys Asn Leu Arg Leu Pro Gly
100 105 110

Ser Ser Asp Ser Pro Ala Ser Ala Ser Gln Val Thr Gly Ile Thr Gly
115 120 125

Val Pro Arg Pro Arg Pro Arg
130 135

<210> 34
<211> 90
<212> PRT
<213> Homo sapien

<400> 34

Leu Arg Trp Ser Leu Ala Leu Ser Pro Arg Leu Glu Cys Ser Gly Ala
1 5 10 15

Ile Leu Ala His Cys Asn Leu Cys Leu Pro Ser Ser Ser Asp Ser Pro
20 25 30

Ala Ser Ala Ser Gln Val Ala Gly Ile Thr Gly Ala His His His Val
35 40 45

Gln Leu Ile Phe Val Phe Leu Val Glu Thr Gly Phe Arg His Val Gly
50 55 60

Ala Ala Ala Leu Glu Leu Leu Thr Ser Gly Asp Pro Pro Thr Ser Ala
65 70 75 80

Ser Gln Ser Ala Gly Ile Thr Gly Val Thr
85 90

<210> 35
<211> 218
<212> PRT
<213> Homo sapien

<400> 35

Met Gly Val Pro Ile Leu Leu Asp Ala Arg Ser Ser Pro Thr Pro Thr

1 5 10 15

Pro Ala Ala Ser Pro Arg Val Pro Val Val Tyr Asp Ser Leu Arg Pro
20 25 30

Pro Arg Arg Pro Gly Pro Gln His Leu Pro Tyr Phe Val Pro Pro Pro
35 40 45

Asn Phe Trp Gly Ala Pro Tyr Leu Leu Pro Ala Arg Pro Trp Pro Leu
50 55 60

Phe Thr Ala Phe Gly Arg Ser Pro Ser Val Cys Pro Cys Ser Arg Ser
65 70 75 80

His Gly Cys Phe Ser Ser Pro Ala Pro Pro Pro Thr Thr His Leu Phe
85 90 95

Cys Pro Val Ser Cys Pro Gln Ala Pro Ser Gly Thr Pro Phe Arg Arg
100 105 110

Glu Thr Leu Gly Asp Glu Cys Pro Pro Ala Thr Ser Met Pro Pro Ala
115 120 125

Pro Cys Pro Ile Pro Glu Ile Phe Arg Gln Tyr Leu Lys Trp Val Pro
130 135 140

Leu Met Asn Arg Gly Ile Pro Trp Gly Asn Pro Thr Arg Gly Ile Trp
145 150 155 160

Ala Pro Phe Gln Cys Gly Glu Lys Lys Lys Phe Trp Leu Cys Pro Pro
165 170 175

Leu Asn His Lys Lys Lys Lys Lys Lys Lys Lys Lys Ser Thr Ala Ala
180 185 190

Ala Thr Thr Ile His His Thr Ala Pro Leu Glu His Ala Ser Arg Met
195 200 205

Asn His Gly Pro Ile Cys Leu Ser Phe Ser
210 215

<210> 36
<211> 61
<212> PRT
<213> Homo sapien

<400> 36

Met Thr Gly Ile Thr Leu Asn Ile Cys Arg His Leu Cys Asn Leu Ser
1 5 10 15

Arg Val Asn Leu Thr Phe Arg Asn Cys Val Phe His Ser Arg Met Val
20 25 30

Met Ile Leu Gly Cys Asp Ile Trp Asp Leu Pro Thr Met Gly Thr Leu
35 40 45

Asp Lys Met Asn Thr Asp Glu Pro Thr Asp Leu Cys Tyr
50 55 60

<210> 37
<211> 56
<212> PRT
<213> Homo sapien

<400> 37

Met Ala His Cys Ser Leu Asn Leu Leu Gly Ser Ser Asn Pro Ser Val
1 5 10 15

Ser Val Pro Gln Val Thr Arg Thr Thr Gly Met Cys His His Trp Leu
20 25 30

Phe Phe Cys Leu Phe Phe Glu Thr Thr Ser Tyr Tyr Val Ala Gln Ala
35 40 45

His Leu Glu Ala Pro Gly Leu Lys
50 55

<210> 38
<211> 96
<212> PRT
<213> Homo sapien

<400> 38

Phe Phe Phe Phe Phe Ala Gly Lys Val Ser Leu Ser Pro Lys Leu Glu
1 5 10 15

Cys Ser Gly Thr Val Met Ala His Cys Ser Leu Asn Leu Leu Gly Ser
20 25 30

Ser Asn Pro Ser Val Ser Val Pro Gln Val Thr Arg Thr Thr Gly Met
35 40 45

Cys His His Trp Leu Phe Phe Cys Leu Phe Phe Glu Thr Thr Ser Tyr
50 55 60

Tyr Val Ala Gln Ala His Leu Lys Leu Leu Gly Ser Ser Asp Pro Pro
65 70 75 80

Ser Ala Ser Ala Ser Gln Asn Ala Cys Asp Tyr Arg Gly Val Ser His
85 90 95

<210> 39
<211> 76
<212> PRT
<213> Homo sapien

<400> 39

Met Leu Pro Pro Leu Cys Phe Tyr Gln Leu Ser Arg Val Phe Ala Ser
1 5 10 15

Trp Leu Ile Lys Val Leu Val Gly Gly Gly Asn Val Cys Glu Ser Pro
20 25 30

Gly Asp Asp Asn Pro Thr Trp Phe Asn Ser Pro Thr Gly Gly Ser Pro
35 40 45

Pro Lys Trp Pro His Arg Gly Asn Pro Gln Ala Leu Leu Ala Leu Tyr
50 55 60

Cys Cys Val Val Phe Val Val Lys Phe Leu Val Tyr
65 70 75

<210> 40
<211> 146
<212> PRT
<213> Homo sapien

<400> 40

Ala Leu Ile Val Leu Gly Leu Val Leu Leu Ser Val Thr Val Gln Gly
1 5 10 15

Lys Val Phe Glu Arg Cys Glu Leu Ala Arg Thr Leu Lys Arg Leu Gly
20 25 30

Met Asp Gly Tyr Arg Gly Ile Ser Leu Ala Asn Trp Met Cys Leu Ala
35 40 45

Lys Trp Glu Ser Gly Tyr Asn Thr Arg Ala Thr Asn Tyr Asn Ala Gly
50 55 60

Asp Arg Ser Thr Asp Tyr Gly Ile Phe Gln Ile Asn Ser Arg Tyr Trp
65 70 75 80

Cys Asn Asp Gly Lys Thr Pro Gly Ala Val Asn Ala Cys His Leu Ser
85 90 95

Cys Ser Ala Leu Leu Gln Asp Asn Ile Ala Asp Ala Val Ala Cys Ala
100 105 110

Lys Arg Val Val Arg Asp Pro Gln Gly Ile Arg Ala Trp Val Ala Trp
115 120 125

Arg Asn Arg Cys Gln Asn Arg Asp Val Arg Gln Tyr Val Gln Gly Cys
130 135 140

Gly Val
145

<210> 41
<211> 34
<212> PRT
<213> Homo sapien

<400> 41

Met Arg Lys Glu Ser Ala Asp Val Gly Tyr Asn Gly Ile Leu Ala Arg
1 5 10 15

Leu Trp Cys Gln Trp Ile Leu His Pro Thr Thr Ser Pro Cys Lys Ala
20 25 30

Lys Leu

<210> 42
<211> 80
<212> PRT
<213> Homo sapien

<400> 42

Met Phe Ala Cys Val Cys Cys Phe Gly Val Trp Cys Val Phe Gly Phe
1 5 10 15

Gly Val Val Cys Phe Val Phe Thr Leu Trp Phe Val Thr Glu Asn Trp
20 25 30

Gly Glu Trp Glu Pro Gly Asn Lys Ile Ser Thr Pro Arg Glu Pro Ala
35 40 45

Phe Gly Pro Gly Tyr Pro Gln Arg Leu Phe Phe Val Phe Cys Cys Val
50 55 60

Phe Phe Pro Val Asn Thr Lys Glu Gln Ile Phe Ile Glu Leu Val Gln
65 70 75 80

<210> 43
<211> 227
<212> PRT
<213> Homo sapien

<400> 43

Thr Ser Gln Ala Asn Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val
1 5 10 15

Lys Thr Ile Thr Val Ser Ala Asp Val Pro Lys Pro Ser Ile Ser Ser
20 25 30

Asn Asn Ser Lys Pro Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys
35 40 45

Glu Pro Glu Ala Gln Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln
50 55 60

Ser Leu Pro Val Ser Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr
65 70 75 80

Leu Thr Leu Phe Asn Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys
85 90 95

Gly Ile Gln Asn Ser Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu
100 105 110

Asp Val Leu Tyr Gly Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser
115 120 125

Ser Tyr Leu Ser Gly Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser
130 135 140

Asn Pro Ser Pro Gln Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln
145 150 155 160

His Thr Gln Val Leu Phe Ile Ala Lys Ile Thr Pro Asn Asn Asn Gly
165 170 175

Thr Tyr Ala Cys Phe Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser
180 185 190

Ile Val Lys Ser Ile Thr Val Ser Ala Ser Arg Thr Ser Pro Gly Leu
195 200 205

Ser Ala Gly Ala Thr Val Gly Ile Met Ile Gly Val Leu Val Gly Val
210 215 220

Ala Leu Ile
225

<210> 44
<211> 119
<212> PRT
<213> Homo sapien

<400> 44

Met Leu Glu Arg Arg Ser Val Met Asp Phe Phe Phe Phe Phe Phe Phe
1 5 10 15

Phe Phe Phe Phe Phe Phe Phe Phe Phe Phe Leu Asn Pro Phe Phe Ser
20 25 30

Pro Pro Gly Gly Gly Val Val Gly Ser Ser Lys His Gln Ala Gln Glu
35 40 45

Glu Leu Gly Cys Val Pro Phe Leu Ala Ile Val Pro Pro Leu Glu Asn
50 55 60

Asn Thr Ser Thr Ile Phe His Leu Pro His Lys Ala Gly Gly Cys Thr
65 70 75 80

Ser Val Ala His Ile Val Val Ile Pro Val Val Cys Lys Ser Gly Leu
85 90 95

Leu Arg His Pro Ile Leu Pro Gln Asn Ile Ser Lys Lys Leu His Glu
100 105 110

His Asn Thr Pro Val Thr Arg
115

<210> 45
<211> 105
<212> PRT
<213> Homo sapien

<400> 45

Met Ser Val Ala Ser Val Pro Leu Gln Cys Asp Asp Val Arg Ser Leu
1 5 10 15

Gln Ala Leu Asn Ala Cys Pro His Met Ser Tyr Leu Cys Cys Gly Thr
20 25 30

Ser His Arg Gly Gln Ile Val Glu Ile Tyr Arg Val Thr Trp Tyr Leu
35 40 45

Leu Val Asn Cys Thr Thr Asn Ala Pro Val Tyr Met Gln Cys Ile Gly
50 55 60

Ile Val Lys Lys Phe Cys Pro Leu Pro Cys Ser His Gly Glu His Asn
65 70 75 80

Arg Gln Phe Ser Ser Pro Val Val His Leu Glu Gln Tyr Thr Ala Leu
85 90 95

Phe Ala Ile Asn Ile Tyr Arg Asn Ile
100 105

<210> 46
<211> 79
<212> PRT
<213> Homo sapien

<400> 46

Met Gly Pro Arg Leu Ser Gln Arg Pro Gly Ile Pro Pro Ile Leu Ser
1 5 10 15

Asn Asn Val Arg Val Leu Ser Leu Cys Leu Pro Ala Ile Val Ala Thr
20 25 30

Leu Leu Cys Arg Pro Glu Cys Ala Trp Ser Ser Leu Val Val Ala Leu
35 40 45

Asn Phe Phe Ser Leu Thr Thr Thr Glu Gly Cys Ala Val Ala Ser Ala

50 55 60

Thr Leu Trp Glu Pro Gln Arg Gly Leu Thr Glu Arg Trp Gly Arg
65 70 75

<210> 47
<211> 74
<212> PRT
<213> Homo sapien

<400> 47

Met Cys Leu Cys Gly Gly Asp Phe Met Cys Val Gly Arg Gly Ser Asp
1 5 10 15

Thr His Ser Val Cys Arg Thr Pro Pro Gly Gly His Tyr Arg Ser Phe
20 25 30

Leu Arg Pro Leu Ser Gly Thr Leu Ala Ser Glu Leu Cys Cys Tyr Leu
35 40 45

Ser Leu Phe Phe Val Cys Phe Leu Tyr Ser Phe Ser Leu Ser Leu Val
50 55 60

Tyr Gly Gln Asn Ser Ser Arg Leu Ser Met
65 70

<210> 48
<211> 59
<212> PRT
<213> Homo sapien

<400> 48

Met Phe Cys Gln Cys Cys Ser Cys Val Val Met Val Leu Arg His Leu
1 5 10 15

Thr Ser Ala Phe Phe Ala Val Pro Gly Ala Phe Cys Leu Ala Ser Phe
20 25 30

Val Ser Thr Cys Cys Leu Ser Val Leu Leu Phe Ser Arg Asp Ser Arg
35 40 45

Gly Ile Tyr Arg Ile Tyr Arg Leu Phe Asp Val
50 55

<210> 49
<211> 60

<212> PRT
<213> Homo sapien

<400> 49

Met Pro Glu Ser Asn Gly Pro Arg Ser Asp Arg Gln Thr Arg Val Arg
1 5 10 15

Ala Val Ile Arg Ser Ala Val Glu Gly Gly Arg His Val Gln Tyr Asp
20 25 30

Ala Asp Gln Ile Asp Ala Asn Asn Trp Ser Lys Cys Ser Thr Thr Lys
35 40 45

Gly Ala Leu Arg Ala Arg Arg His Cys Arg Leu Val
50 55 60

<210> 50
<211> 1134
<212> PRT
<213> Homo sapien

<400> 50

Arg Leu Ala Leu Ser Pro Glu Asp Lys Pro Ile Arg Leu Ser Pro Ser
1 5 10 15

Lys Ile Thr Glu Pro Leu Arg Glu Gly Pro Glu Glu Glu Pro Leu Ala
20 25 30

Glu Arg Glu Val Lys Ala Glu Val Glu Asp Met Asp Glu Gly Pro Thr
35 40 45

Glu Leu Pro Pro Leu Glu Ser Pro Leu Pro Leu Pro Ala Ala Glu Ala
50 55 60

Met Ala Thr Pro Ser Pro Ala Gly Gly Cys Gly Gly Gly Leu Leu Glu
65 70 75 80

Ala Gln Ala Leu Ser Ala Thr Gly Gln Ser Cys Ala Glu Pro Ser Glu
85 90 95

Cys Pro Asp Phe Val Glu Gly Pro Glu Pro Arg Val Asp Ser Pro Gly
100 105 110

Arg Thr Glu Pro Cys Thr Ala Ala Leu Asp Leu Gly Val Gln Leu Thr
115 120 125

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Pro Glu Thr Leu Val Glu Ala Lys Glu Glu Pro Val Glu Val Pro Val
    130                 135                 140

Gly Val Pro Val Val Glu Ala Val Pro Glu Glu Gly Leu Ala Gln Val
145                 150                 155                 160

Ala Pro Ser Glu Ser Gln Pro Thr Leu Glu Met Ser Asp Cys Asp Val
                165                 170                 175

Pro Ala Gly Glu Gly Gln Cys Pro Ser Leu Glu Pro Gln Glu Ala Val
            180                 185                 190

Pro Val Leu Gly Ser Thr Cys Phe Leu Glu Glu Ala Ser Ser Asp Gln
        195                 200                 205

Phe Leu Pro Ser Leu Glu Asp Pro Leu Ala Gly Met Asn Ala Leu Ala
    210                 215                 220

Ala Ala Ala Glu Leu Pro Gln Ala Arg Pro Leu Pro Ser Pro Gly Ala
225                 230                 235                 240

Ala Gly Ala Gln Ala Leu Glu Lys Leu Glu Ala Ala Glu Ser Leu Val
                245                 250                 255

Leu Glu Gln Ser Phe Leu His Gly Ile Thr Leu Leu Ser Glu Ile Ala
            260                 265                 270

Glu Leu Glu Leu Glu Arg Arg Ser Gln Glu Met Gly Gly Ala Glu Arg
        275                 280                 285

Ala Leu Val Ala Arg Pro Ser Leu Glu Ser Leu Leu Ala Ala Gly Ser
    290                 295                 300

His Met Leu Arg Glu Val Leu Asp Gly Pro Val Val Asp Pro Leu Lys
305                 310                 315                 320

Asn Leu Arg Leu Pro Arg Glu Leu Lys Pro Asn Lys Lys Tyr Ser Trp
                325                 330                 335

Met Arg Lys Lys Glu Glu Arg Met Tyr Ala Met Lys Ser Ser Leu Glu
            340                 345                 350

Asp Met Asp Ala Leu Glu Leu Asp Phe Arg Met Arg Leu Ala Glu Val
        355                 360                 365
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Gln Arg Gln Tyr Lys Glu Lys Gln Arg Glu Leu Val Lys Leu Gln Arg
370 375 380

Arg Arg Asp Ser Glu Asp Arg Arg Glu Glu Pro His Arg Ser Leu Ala
385 390 395 400

Arg Arg Gly Pro Gly Arg Pro Arg Lys Arg Thr His Ala Pro Ser Ala
405 410 415

Leu Ser Pro Pro Arg Lys Arg Gly Lys Ser Gly His Ser Ser Gly Lys
420 425 430

Leu Ser Ser Lys Ser Leu Leu Thr Ser Asp Asp Tyr Glu Leu Gly Ala
435 440 445

Gly Ile Arg Lys Arg His Lys Gly Ser Glu Glu Glu His Asp Ala Leu
450 455 460

Ile Gly Met Gly Lys Ala Arg Gly Arg Asn Gln Thr Trp Asp Glu His
465 470 475 480

Glu Ala Ser Ser Asp Phe Ile Ser Gln Leu Lys Ile Lys Lys Lys Lys
485 490 495

Met Ala Ser Asp Gln Glu Gln Leu Ala Ser Lys Leu Asp Lys Ala Leu
500 505 510

Ser Leu Thr Lys Gln Asp Lys Leu Lys Ser Pro Phe Lys Phe Ser Asp
515 520 525

Ser Ala Gly Gly Lys Ser Lys Thr Ser Gly Gly Cys Gly Arg Tyr Leu
530 535 540

Thr Pro Tyr Asp Ser Leu Leu Gly Lys Asn Arg Lys Ala Leu Ala Lys
545 550 555 560

Gly Leu Gly Leu Ser Leu Lys Ser Ser Arg Glu Gly Lys His Lys Arg
565 570 575

Ala Ala Lys Thr Arg Lys Met Glu Val Gly Phe Lys Ala Arg Gly Gln
580 585 590

Pro Lys Ser Ala His Ser Pro Phe Ala Ser Glu Val Ser Ser Tyr Ser

595 600 605

Tyr Asn Thr Asp Ser Glu Glu Asp Glu Glu Phe Leu Lys Asp Glu Trp
610 615 620

Pro Ala Gln Gly Pro Ser Ser Ser Lys Leu Thr Pro Ser Leu Leu Cys
625 630 635 640

Ser Met Val Ala Lys Asn Ser Lys Ala Ala Gly Gly Pro Lys Leu Thr
645 650 655

Lys Arg Gly Leu Ala Ala Pro Arg Thr Leu Lys Pro Lys Pro Ala Thr
660 665 670

Ser Arg Lys Gln Pro Phe Cys Leu Leu Leu Arg Glu Ala Glu Ala Arg
675 680 685

Ser Ser Phe Ser Asp Ser Ser Glu Glu Ser Phe Asp Gln Asp Glu Ser
690 695 700

Ser Glu Glu Glu Asp Glu Glu Glu Glu Leu Glu Glu Glu Asp Glu Ala
705 710 715 720

Ser Gly Gly Gly Tyr Arg Leu Gly Ala Arg Glu Arg Ala Leu Ser Pro
725 730 735

Gly Leu Glu Glu Ser Gly Leu Gly Leu Leu Ala Arg Phe Ala Ala Ser
740 745 750

Ala Leu Pro Ser Pro Thr Val Gly Pro Ser Leu Ser Val Val Gln Leu
755 760 765

Glu Ala Lys Gln Lys Ala Arg Lys Lys Glu Glu Arg Gln Ser Leu Leu
770 775 780

Gly Thr Glu Phe Glu Tyr Thr Asp Ser Glu Ser Glu Val Lys Val Arg
785 790 795 800

Lys Arg Ser Pro Ala Gly Leu Leu Arg Pro Lys Lys Gly Leu Gly Glu
805 810 815

Pro Gly Pro Ser Leu Ala Ala Pro Thr Pro Gly Ala Arg Gly Pro Asp
820 825 830

Pro Ser Ser Pro Asp Lys Ala Lys Leu Ala Val Glu Lys Gly Arg Lys
835 840 845

Ala Arg Lys Leu Arg Gly Pro Lys Glu Pro Gly Phe Glu Ala Gly Pro
850 855 860

Glu Ala Ser Asp Asp Asp Leu Trp Thr Arg Arg Arg Ser Glu Arg Ile
865 870 875 880

Phe Leu His Asp Ala Ser Ala Ala Ala Pro Ala Pro Val Ser Thr Ala
885 890 895

Pro Ala Thr Lys Thr Ser Arg Cys Ala Lys Gly Gly Pro Leu Ser Pro
900 905 910

Arg Lys Asp Ala Gly Arg Ala Lys Asp Arg Lys Asp Pro Arg Lys Lys
915 920 925

Lys Lys Gly Lys Glu Ala Gly Pro Gly Ala Gly Leu Pro Pro Pro Arg
930 935 940

Ala Pro Ala Leu Pro Ser Glu Ala Arg Ala Pro Pro Pro Pro Pro Pro
945 950 955 960

Pro Pro Pro His Pro Pro Leu Pro Pro Pro Pro Leu Pro Pro Pro Pro
965 970 975

Leu Pro Leu Arg Leu Pro Pro Leu Pro Pro Pro Pro Leu Pro Arg Pro
980 985 990

His Pro Pro Pro Pro Pro Pro Leu Pro Pro Leu Leu Pro Pro Pro Gln
995 1000 1005

Thr Arg Thr Leu Pro Ala Ala Arg Thr Met Arg Gln Pro Pro Pro
1010 1015 1020

Pro Arg Leu Ala Leu Pro Arg Arg Arg Arg Ser Pro Pro Arg Pro
1025 1030 1035

Pro Ser Arg Pro Ala Arg Arg Gly Pro Arg Pro Thr Pro Gln Ala
1040 1045 1050

Arg Arg Arg Pro Arg Pro Ser Pro Arg Arg Leu Leu Arg Ser Pro
1055 1060 1065

His Ser Leu Cys Ser Pro Arg Leu Arg Pro Gly Pro Arg Ala Asp
1070 1075 1080

Pro Arg Arg Glu Arg Ala Ser Thr Ser Pro Pro Pro Arg Ser Trp
1085 1090 1095

Pro Ser Gly Ser Ala Cys Arg Pro Trp Arg Thr Gly Pro Arg Ser
1100 1105 1110

Pro Pro Ser Cys Gln Pro Gly Ser Ser Gly Ser Gly Ser Ala Ser
1115 1120 1125

Pro Pro Ser Gly Val Ala
1130

<210> 51
<211> 29
<212> PRT
<213> Homo sapien

<400> 51

Met Gly Arg Cys Val Ser Leu Thr Ser Val Ile Ile Phe Asp Ile Leu
1 5 10 15

Ser Val Tyr Tyr Glu Thr Leu Ala Ser Leu Gln Ile Phe
20 25

<210> 52
<211> 161
<212> PRT
<213> Homo sapien

<400> 52

Val Ala Ile Pro Pro Leu Thr His Asn Leu Ser Ala Val Ala Pro Ser
1 5 10 15

Ile Asn Ser Gly Met Gly Thr Glu Thr Ile Pro Ile Gln Gly Tyr Arg
20 25 30

Val Asp Glu Lys Thr Lys Lys Cys Ser Ile Pro Phe Val Lys Pro Asn
35 40 45

Arg His Ser Pro Ser Gly Ile Tyr Asn Ile Asn Val Thr Thr Leu Val
50 55 60

Ser Ser Glu Lys Asn Leu Leu Trp Ala Ser Lys Lys Arg Arg Glu Tyr
65 70 75 80

Ser Arg Thr Asp Val Arg Leu Pro Glu Leu Asn Tyr Asn His Leu Pro
85 90 95

Glu Leu Arg Ala Leu Gly Gly Ile Ala Arg Asn Ser Arg Leu Thr Lys
100 105 110

Lys Glu Ser Lys Ile Leu Ser Glu Ser Arg Ile Pro Ser Leu Ala Ala
115 120 125

Ile Asp Leu His Thr Pro Ser Ile Thr Leu His Gln Val Ser Gly Pro
130 135 140

Pro Leu Ser Asp Asp Ser Gly Ala Asp Leu Pro Gln Met Glu His Gln
145 150 155 160

His

<210> 53
<211> 33
<212> PRT
<213> Homo sapien

<400> 53

Met Asn Tyr Cys Leu Lys Thr Ser Ser Thr Ser Gln Ser Thr Thr Ala
1 5 10 15

Thr Ser Ile Cys Lys Asn His Tyr Leu Leu Tyr Val Leu Trp Tyr Leu
20 25 30

Gly

<210> 54
<211> 89
<212> PRT
<213> Homo sapien

<400> 54

Met Val Ser Ile Lys Ser Leu Leu Phe Glu Ser Tyr Val His Gly Pro
1 5 10 15

Ala Val Val Arg Phe Ser Ala Leu Gln Leu Pro Asp Thr Phe Gly Arg

20 25 30

Pro Met Ala Glu Arg Thr Arg Leu Ser Pro Gly Val Arg Ala Pro Ala
35 40 45

Trp Ala Thr Tyr Val Gly Thr Pro Ser Arg Gly Phe Leu Leu Leu Tyr
50 55 60

Glu Lys Lys Gln Ile Ser Val Ala Lys Thr Leu Leu Gln Thr Thr Arg
65 70 75 80

Glu Ala His Arg Asn Thr Val Ser Tyr
85

<210> 55
<211> 110
<212> PRT
<213> Homo sapien

<400> 55

Met Val Gln His Arg Cys Met Leu Glu Arg Arg Val Val Met Asp Ala
1 5 10 15

Trp Ser Arg Pro Arg Tyr Ser Thr Ser Asn Phe Pro Arg Asn Gln Lys
20 25 30

Asn Gly Glu Gln Val Leu Val Ser Gln Tyr Ser Ala Ser Val Tyr Thr
35 40 45

Leu Gly Gln Gly Gln Ile Phe Pro Gly Glu Gly Phe Tyr His Cys His
50 55 60

His Leu Glu Ile Leu His Arg Leu Glu His Arg Ala Ile Asp Phe His
65 70 75 80

Phe Cys Thr Gln Leu Cys Ser Glu Thr Gly Ala Ile Gly Val Leu Gly
85 90 95

Glu Thr Gly Gln Met Glu Glu Val Glu Gly Ile Cys Thr Leu
100 105 110